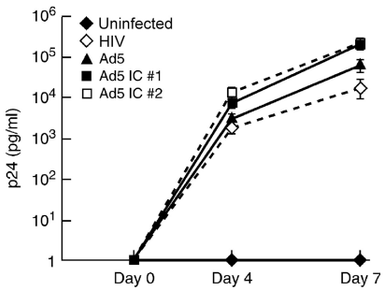


AD5-antibody complexes (Ad5 IC) augment HIV replication in human cells.

Adenovirus antibodies assist HIV

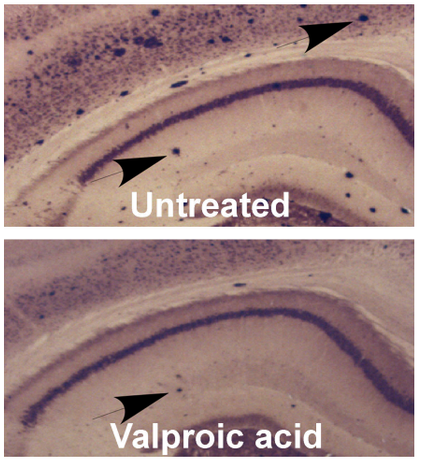
Antibodies against a vaccine vector render T cells more susceptible to HIV-1 infection, say Perreau et al. on page 2717. Their results may help explain the failure of a recent HIV vaccine trial.

The HIV-1 vaccine used in Merck's STEP trial relied on a weakened form of a common cold virus, Adenovirus 5 (Ad5), to carry bits of HIV into the body. One worry about the Ad5 vector was that widespread immunity to adenoviruses might cause the vaccine to be ousted before an anti-HIV response could develop. Instead, there was a chance that vaccine recipients who had circulating antibodies against Ad5 were contracting the virus more often, one factor that forced termination of the trial.

Perreau et al. now show that HIV spread through T cell–dendritic cell (DC) co-cultures three times as fast when Ad5 and neutralizing antiserum—present in people with prior immunity—was added to the cultures. Ad5-antibody complexes triggered DC maturation in the presence of Fcγ receptors (FcγR) and Toll-like receptor (TLR)–9. The authors suspect that FcγR facilitated the uptake of Ad5-antibody complexes into the cell, where viral components could then activate TLR9 to trigger DC maturation and activation.

The mature DCs activated both $CD4^+$ and $CD8^+$ T cells, which may have assisted HIV infection in two ways. Activated $CD4^+$ cells could provide HIV with more cells to infect. And activated Ad5-specific $CD8^+$ T cells could attack infected DCs, thereby reducing the pool of DCs presenting HIV antigens. Indeed, weaker HIV-specific CD8 responses were seen in Ad5-seropositive individuals in response to vaccination.

Merck's vaccine may have made it to phase 2 trials because nonhuman primates don't naturally come in contact with human adenoviruses, and therefore the potential problem went unrecognized. **AM**



Valproic acid treatment reduced Aβ plaques (arrows) in the brains of mice with Alzheimer's-like disease.

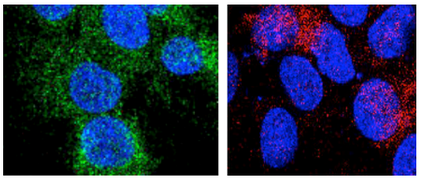
Acid to remember

A popular epilepsy drug may also be beneficial in patients with Alzheimer's disease (AD), if the findings on page 2781 hold true in clinical trials. Qing et al. improved memory and ameliorated brain plaques in mice with an AD-like disease by injecting them with the anti-seizure drug valproic acid.

Mice with the AD-like disease typically develop amyloid-rich brain plaques after six months. When Qing et al. treated the mice with valproic acid soon after plaque formation, the plaques shrank and some of the damaged axons in their brains resumed growth. The drug also improved performance in memory tests.

The acid worked by inhibiting the activity of glycogen synthase kinase-3β (GSK-3β), which normally turns on γ-secretase—the enzyme that cleaves β-amyloid precursor proteins. Lithium chloride, another drug used in patients with AD, also curbs amyloid-β production by inhibiting GSK-3α and GSK-3β, and has recently been shown to ameliorate axonal damage.

Valproic acid helped mice less as their disease progressed. The authors thus suggest that clinical trials should focus on people with early signs of AD. Valproic acid has been given to people with AD in the past but, unfortunately, memory improvement was never assessed in those studies. **AM**



Estrogen loss triggers the production of IL-18 (green) and IFN-γ (red) by epithelial cells in human salivary glands.

Epithelial cells as APCs

Epithelial cells masquerading as antigen-presenting cells (APCs) may lead to autoimmune disease, as shown by Ishimaru et al. on page 2915. The findings suggest that Sjögren's syndrome stems from salivary gland epithelial cells that make interferon (IFN)-γ and then present self-antigens.

During Sjögren's syndrome, the body's immune cells attack moisture-producing cells in salivary glands and tear ducts. The destruction of these cells is initiated by estrogen loss during menopause via the induction of a chromatin-modifying protein called RbAp48, which triggers p53-dependent cell death.

The timing of mouse menopause is difficult to pin down, so to better understand RbAp48's role, the group created mice that overexpress RbAp48 in gland cells. They now find that these mice develop symptoms resembling Sjögren's syndrome.

Epithelial cells from transgenic salivary glands produced IL-18 and IFN-γ, which then induced the expression of MHC class II molecules. These cytokines also stimulated the proliferation of